IN THE SPECIFICATION:

Please amend page 5, lines 3-5 as follows:

For unregulated expression constitutive promoters are either derived from viral promoters ~~of~~ or from strong cellular promoters.

Please amend page 5, lines 12-15, to read as follows:

In one aspect the present invention provides a promoter-transactivator system for inducible high-level mammalian cell gene expression with the option of cell growth control ~~as defined in claim 1~~ comprising

(a) a promoter construct (IRFE promoter) having the general structure:

[MPSV-E]-[IRF-1-binding sites]-[CMV]—DNA, wherein → mRNA

MPSV-E means MPSV enhancer repeats of the sequence:

GCTAGCTTAAGTAACGCCATTTTGCAAGGCATGGGAAAAATACATAACTGAGAATAGAGAAG
TTCAGATCAAGGTCAGGAACAGAGAAACAGGAGAATATGGGCCAAACAGGATATCTGTGGTA
AGCAGTTCCTGCCCCGCTCAGGGCCAAGAACAGTTGGAACAGGAGAATTGGGCCAAACAGGA
TATCTGTGGTAAGCAGTTCCTGCCCCGCCTCAGGGCCAAGAACAGATGGTCCCCAGATGCGGT
CCCGCCCTCAGCAGTTTCTAGA,

or isofunctional variants thereof obtained by substitution, insertion or deletion of one or more nucleotides,

IRF-1-binding sites means the sequence:

GATCCCTTCTCGGGAAATGGAAACTGAAAATCAGATCCCTTCTCGGGAAATGGAAACTGAAA
ATCAGATC,

or isofunctional variants thereof obtained by substitution, insertion or deletion of one or more nucleotides, and

CMV means a minimal promoter of the sequence:

TGGCGTGTACGGTGGGAGGCCTATATAAGCAGAGCTCGTTTAGTGAACCGTCAAACCGTCAAACCGCGGAAGCT,

or isofunctional variants thereof obtained by substitution, insertion or deletion of one or more nucleotides,

and

(b) a transactivator construct coding for a fusion protein comprising IRF-1 and the estrogen receptor.

Please amend page 5, lines 16-22, to read as follows:

In a further aspect the present invention provides an expression vector (s) comprising a promoter construct and/or a transactivator construct as defined ~~in claim 1~~ above (i.e. said promotor construct and said transactivator construct may be incorporated in the same expression vector thus containing said ~~a~~ promoter-transactivator system or may be incorporated in separate expression vectors).

Please amend page 5, lines 25-27, to read as follows:

In yet another aspect the present invention provides a process for inducible high-level mammalian gene expression with the option of cell growth control ~~as defined in claim 4~~ comprising the steps of:

(a) transfecting or transforming mammalian cells with the expression vector of claim 2;

(b) culturing said mammalian cells in a suitable medium; and,

(c) optionally, controlling the growth of said mammalian cells by varying the concentration and the duration of exposure to estradiol in the medium.

Please amend page 6, lines 2-4 as follows:

It consists of a regulated transcriptional activator IRF-1 and an inducible promoter for high-level recombinant gene expression.

Please amend page 6, lines 23-26 as follows:

1) A regulated promoter that shows a higher maximal secreted pharmaceutical protein productivity than a contemporary highly efficient viral promotor (MPSV, myeloproliferative sarcoma virus).

Please amend page 6, lines 31-35 as follows:

2) BHK-21 cell lines that expresses an IRF-1-human estrogen receptor (hER) construct whose expression is stabilized by a dicistronic expression construct with a drug resistance gene (puromycin acetyltransferase) as a selection marker (Figure 3).

Please add the following on page 9, line 13:

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in further detail with respect to the accompanying figures in which:

Figure 1 shows a regulated promoter that shows a higher maximal secreted pharmaceutical protein productivity than a contemporary highly efficient viral promotor (MPSV, myeloproliferative sarcoma virus). The artificial promoter consists f viral enhancer repeats (MSPV), of IRF-1-binding sites (ISRE-luc, Interferon Stimulated Response Element-firefly luciferase: Kichhoff and Hauser, 1999) and of a viral minimal promoter element (CMV, cytomegalo virus).

B9 cont'd

Please delete page 14, lines 5 -page 15 line 8 as follows:

~~Examples for specific applications in industrial relevant systems.~~

~~Figures 10 and 11 relate to two examples of a relevant pharmaceutical protein expressing BHK (baby hamster kidney) cell clones with IRF-hER enhanced productivity (pg/cell/day, E2) versus control (pg/cell/day, ctrl) and reduced proliferation (living cells x 10e5/ml, E2) versus controll (living cells, ctrl).~~

~~The following is one example for increased IgG antibody productivity in a long term experiment in IRF-hER proliferation controlled BHK-21 cells in a perfused fermenter with microcarriers showing also high viability. For additional characterization of lesser importance glucose consumption and lactate production was determined.~~

~~Name: Fermenter 3~~

~~Conditions: IgG 8 cells, Cytodex 3 microcarrier, 6g/1, medium for all fermenters: DMEM: F12 with 5% serum and 500 ug/ml G418 and 3 ug/ml Puro (with added dextran and Pluronic)~~

~~Fermenter: New Brunswick, stirred tank, 5 l tank capacity, 3.5 1 working volume, settling tube as separator (a glass tube in which the microcarriers settle down by gravitational action) while the medium is removed. Works effective up to a perfusionrate of 1 volume/day (also 3.5 1/day). For higher values gravitational action is not sufficient to compensate sucking action.~~

~~At the end of the induction stirring was stopped for 20 min. After the microcarriers have settled down the medium was removed by suction except for 0.5 1, added up to 2 1 (=wash), again removed by suction except for 0.5 1 and added up to 3.5 1. Approximately 7% of the initial content of E2 remains (since, however, during induction perfusion was activated, the actual value for E2 was below 7%). The washing procedure took about 1-1.5 h.~~

~~In all fermenters the perfusion rate was in the range from 0 to 0.9, wherein most of the time the rate was in the range 0.6 to 0.9.~~

Please add the following on page 15, line 12:

B10

DETAILED DESCRIPTION OF THE INVENTION

Examples for specific applications in industrial relevant systems.

Figures 10 and 11 show the results of to two examples of a relevant pharmaceutical protein expressing BHK (baby hamster kidney) cell clones with IRF-hER enhanced productivity (pg/cell/day, E2) versus control (pg/cell/day, ctrl) and reduced proliferation (living cells x 10e5/ml, E2) versus control (living cells, ctrl).

The following is one example for increased IgG antibody productivity in a long-term experiment in IRF-hER proliferation controlled BHK-21 cells in a perfused fermenter with microcarriers showing also high viability. For additional characterization of lesser importance glucose consumption and lactate production was determined (Figure 12).

B10

Name: Fermenter 3

Conditions: IgG 8 cells, Cytodex 3 microcarrier, 6g/1, medium for all fermenters: DMEM: F12 with 5% serum and 500 ug/ml G418 and 3 μg/ml Puro (with added dextran and Pluronic).

Fermenter: New Brunswick, stirred tank, 5 l tank capacity, 3.5 1 working volume, settling tube as separator (a glass tube in which the microcarriers settle down by gravitational action) while the medium is removed. Works effective up to a perfusionrate of 1 volume/day (also 3.5 1/day). For higher values gravitational action is not sufficient to compensate sucking action.
At the end of the induction stirring was stopped for 20 min. After the microcarriers have settled down the medium was removed by suction except for 0.5 1, added up to 2 1 (=wash), again removed by suction except for 0.5 1 and added up to 3.5 1. Approximately 7% of the initial

content of E2 remains (since, however, during induction perfusion was activated, the actual value for E2 was below 7%). The washing procedure took about 1-1.5 h.

B10 cont'd

In all fermenters the perfusion rate was in the range from 0 to 0.9, wherein most of the time the rate was in the range 0.6 to 0.9.

Please amend page 15, line 9 as follows:

Figure 12 shows the results, of an example for increased IgG antibody productivity in a long-term experiment in IRF-hER proliferation controlled BHK-21 cells in a perfused fermenter with microcarriers showing also high viability. For additional characterization of lesser importance glucose consumption and lactate production was determined.

B12

Please amend page 22, line 1 as follows:

~~Claims~~

We claim: